REMARKS

In accordance with the present invention, there are provided novel solutions useful for the introduction and washout of vitrifiable concentrations of cryoprotectants in a cell, tissue or organ, and methods for the use thereof. Invention solutions comprise carrier solutions comprising at least mannitol and lactose, optionally containing one or more of:

-vitrifiable concentrations of cryoprotectant,

-polymers selected from polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol, and a copolymer of vinyl alcohol and vinyl acetate,

-glucose,

-bicarbonate,

-as well as additional components such as phosphates, alkali halides, alkaline earth halides, purines, and the like.

By the present communication, claims 1, 3, 4, 6, 7, 10, 13, 15, 22, 25-30, 32 and 36 have been amended, and new claims 38-46 have been added to define Applicants' invention with greater particularity. In view of the amendments submitted herewith, claims 8, 9, 19-21, 31, 33-35 and 37 have been cancelled. Note that more claims have been cancelled (10) than have been added (9). Thus, fewer claims are now presented for prosecution than were pending before the present communication.

No new matter has been introduced by the subject amendments as all amended claim language is fully supported by the specification and original claims. The amendments provided herewith are submitted to place the present claims in condition for allowance, or at a minimum, in better condition for appeal. Accordingly, entry of the amendments submitted herewith is respectfully requested.

Indeed, each of claims 3, 4, 6, 10, 13, 15, 22, 25, 26, 30, 32 and 36 (which are indicated to be allowable at page 4 of the Office Action) have either been re-written in independent form,

incorporating all of the requirements of any intervening claims (i.e., claims 3, 4, 6, 10, 13, 22, 25 and 26), or they depend from a claim so amended (i.e., claims 15, 32 and 36). Accordingly, each of these claims are submitted to be in condition for allowance.

In view of the amendments submitted herewith, claims 1-4, 6, 7, 10, 13, 15, 22, 25-30, 32, 36 and 38-46 remain pending. The present status of all claims in this application is provided in the listing of claims presented herein beginning on page 2 of this communication.

Election/Restrictions

The withdrawal of claim 37 from consideration is acknowledged. To reduce the issues and facilitate prosecution, claim 37 has been cancelled.

Claim Rejections—35 USC § 112

New Matter

The rejection of claim 7 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention, is respectfully traversed, and has been rendered moot by the amendments submitted herewith.

Indefinite

The rejection of claims 27-29 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is respectfully traversed, and has been rendered moot by the amendments submitted herewith. Thus, the objected to terminology has been replaced with the generic chemical description to which the trademark term (X1000) refers, consistent with the usage throughout the claims.

Claim Rejections—35 U.S.C. § 102

The rejection of claims 1, 2, 7 and 19 under 35 U.S.C § 102(b) as allegedly being anticipated by JP 1-106826 is respectfully traversed. This rejection, as it applies to claim 19, has been rendered moot by the cancellation of this claim.

Applicant's invention, as defined, for example, by claim 1, distinguishes over '826 by requiring an improved carrier solution compatible with the antinucleating effects of polyglycerol, polyvinyl alcohol, or a copolymer of vinyl alcohol and vinyl acetate in the presence of vitrifiable concentrations of cryoprotectants, and capable of being used for the introduction and washout of vitrifiable concentrations of cryoprotectants in a viable cell, tissue or organ, the improvement comprising inclusion of mannitol and lactose in the solution.

'826 does not disclose any such compositions. Instead '826 is directed to blood-preserving solutions. As discussed in greater detail below, blood-preserving solutions are substantially different from solutions used for introduction and removal of vitrifiable concentrations of cryoprotectant in viable cells, tissues, or organs.

Applicant respectfully disagrees with the Examiner's assertion that '826 allegedly "disclose[s] a solution used for the preservation of red cells comprising mannitol, lactose" (see page 3, lines 29-30 of the Office Action). Contrary to the Examiner's assertion, '826 does not disclose a solution comprising mannitol and lactose. Instead, '826 provides "a haemolysis inhibitor ...blended with another blood-preserving solution ingredient." The Examiner's assertion that the abstract of '826 allegedly states that "the inventive solution is made by combining (I) with base liquid of ACD . . . and SAG solution containing mannitol . . . sucrose and lactose," is incorrect. The Examiner is apparently referring to Claim 4 of '826--but resort to the exact language of Claim 4 of '826 reveals the fallacy of the Examiner's interpretation: "The blood preserving solution composition of claim 1 wherein a basic solution selected from the group consisting of ACD solution, CPD solution, CPDA-1 solution, CPDA-2 solution, SAG

solution, and SAG solution made by adding mannitol, maltose, maltitol, sorbitol, sucrose, ***or*** lactose is combined with the monocarboxylic acid ester compound expressed by the general formula (I)" (emphasis added). Thus, '826 suggests, at best, the use of mannitol ***or*** lactose, but in no instance is the combination of mannitol ***and*** lactose suggested, as required by the present claims. None of the standard blood banking solutions, ACD, CPD, CPDA-1, CPDA-2, and SAG, contain either mannitol or lactose. Adding mannitol to SAG does not correct the defect of the omission of lactose.

No specific composition is provided by '826 that contains both lactose and mannitol. Instead, '826 teaches a plurality of solutions, none of which need contain both lactose and mannitol. For example, Claim 3 of '826 allows the hemolysis inhibitor I to be blended with "at least one compound" selected from a list of 12 items, meaning that "one compound" is sufficient. "One compound" could not include both lactose and mannitol. A large number of different solutions could be prepared according to the instructions in claim 3 of '826, but no instruction requires or directs the simultaneous presence of lactose and mannitol. Furthermore, the claim requires the presence of hemolysis inhibitor I, which is not contained in and would be counterproductive to and damaging in the instant invention. Although mannitol and lactose appear in the list of 12 additives mentioned in claim 3 of '826, the vast majority of the solutions that could be prepared by following the instructions of claim 3 would in fact lack both mannitol and lactose. Clearly, no motivation is provided to combine lactose and mannitol.

'826 does not disclose or suggest any combination of lactose and mannitol, either explicitly or by implication based on design, intent, or necessity. The solutions that contain neither lactose nor mannitol are taught by '826 to be equally effective as any solution that might contain either lactose or mannitol or the combination of the two. '826 further actively teaches that any one of several highly dissimilar substances such as NaCl, phosphate, citrate, and sugars are equally effective. This is equivalent to teaching that the combination of lactose and mannitol has no significance. Thus, at best, claim 3 of '826 merely permits by happenstance (or fails to

actively exclude) the combination, but does not consciously prescribe or recognize the unique benefits of the combination required by the present claims.

Applicant further disagrees with the Examiner's assertion that "the prior art solution is capable of being used as a carrier/washout solution because it is disclosed in the prior art as being used with red cells which are a biological entity." (See page 4, lines 19-22 of the Office Action). Contrary to the Examiner's assertion, the alleged prior art "solution" is not clearly capable of being used as a carrier/washout solution for purposes of the present invention because its effects on antinucleators are unknown and may very well be counterproductive, and the components of the solution may well be physically incompatible even with the non-antinucleators of vitrifiable concentrations of cryoprotectants.

While it may be true that red cells are a biological entity, the requirements for preserving red cells are unique in biology and totally inappropriate for almost any other kind of living cell, and certainly totally inappropriate for mammalian organs. The putative prior art "solution" could not be used in the context of Applicant's Claim 1 because it would kill or unacceptably damage most viable cells, tissues, and organs. It also requires the presence of an extraneous and toxic ingredient that has no place in the present invention but that is the central basis of the '826 invention. The lactose and mannitol allegedly provided by '826 are not available in the absence of the other features of '826 which render the provided solutions untenable for use in the present invention.

Moreover, red blood cells have very unique properties and, therefore, contrary to the Examiner's assertions, are not typical representatives of most viable cells, tissues, and organs. Red cells can be kept in blood banks for months, which is not true of any other known cell type or of kidneys, which are far, far harder to preserve. One reason red cells can be more easily preserved is that they are highly impermeable to sodium, unlike virtually all other cells, tissues, and organs, and are highly tolerant of acid pH and calcium chelation. The solutions used to

preserve red blood cells as described in '826 would be bizarre and highly damaging for any cells other than red blood cells. Indeed, as acknowledged by the Examiner, the extraneous toxic and potentially pro-nucleating ester (I) must be combined with a blood-preserving solution such as ACD or SAG. ACD stands for "acid citrate dextrose." The pH of ACD is 5-5.6. A pH of 5-5.6 would be deadly to most cells, tissues, and organs. The citrate level of ACD and the other listed citrated solutions is extremely high in order to chelate all free calcium from the solution. However, calcium is needed for maintaining cell-cell junctions and cell-matrix interactions as well as the basic integrity of most cell membranes, and for these reasons use of the citrate levels contemplated by '826 would be damaging to most cells, tissues, and organs. SAG contains an enormous concentration of sodium chloride that would be highly undesirable and damaging for the hypothermic preservation of almost any viable cell, tissue, or organ in SAG, and also contains no buffer whatsoever, which would be highly dangerous for any cell, tissue, or organ other than red cells.

More generally, the present invention is directed to a carrier solution compatible with use on whole organs, i.e., a carrier that can be used as an organ perfusate. The '826 formulas would not be compatible with the hypothermic perfusion of whole organs. They do not have the well-known necessary characteristics of an organ perfusion solution, which is why no blood banking solution has ever been used for the attempted preservation of whole organs. Further, the teaching of '826 is directed to solutions containing a highly hydrophobic ester that would be expected to be very toxic to most living cells, and especially to organs, particularly in the presence of vitrifiable concentrations of cryoprotectants. It is of note that this molecule is present in all of the solutions provided by '826. Because the present invention requires utility for viable cells, tissues and organs rather than for dead or moribund cells, tissues, and organs, the '826 art clearly fails to satisfy the requirements of Applicant's Claim 1.

Applicant's invention, as defined, for example, by claim 2, further distinguishes over '826 by requiring an improved carrier solution compatible with the antinucleating effects of

polyglycerol, polyvinyl alcohol, or a copolymer of vinyl alcohol and vinyl acetate in the presence of vitrifiable concentrations of cryoprotectants, and capable of being used for the introduction and washout of vitrifiable concentrations of cryoprotectants in a viable cell, tissue or organ, the improvement comprising inclusion of mannitol, lactose and vitrifiable concentrations of cryoprotectant in the solution.

'826, however, does not teach, include, suggest, or imply the use of vitrifiable concentrations of cryoprotectants, whereas Applicant's Claim 2 requires the use of vitrifiable concentrations of cryoprotectants. There is therefore no basis for application of '826 in support of the rejection of Claim 2. The rejection is submitted to be improper and should, therefore, be withdrawn.

Applicant's invention, as defined, for example, by claim 7, still further distinguishes over '826 by requiring an improved carrier solution compatible with the antinucleating effects of polyglycerol, polyvinyl alcohol, or a copolymer of vinyl alcohol and vinyl acetate in the presence of vitrifiable concentrations of cryoprotectants, and capable of being used for the introduction and washout of vitrifiable concentrations of cryoprotectants in a viable cell, tissue or organ, the improvement comprising inclusion of mannitol, lactose and at least one polymer selected from the group consisting of polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol, and a copolymer of vinyl alcohol and vinyl acetate in the solution. '826 does not disclose or suggest any of these specific requirements of claim 7. Accordingly, the claim as presently amended is therefore submitted to be in condition for allowance.

Allowable claims

The indication that claims 3, 4, 6, 10, 13, 15, 20-22, 25, 26 and 30-36 are allowable is acknowledged with appreciation. Each of the claims so acknowledged have either been re-written in independent form, incorporating all of the requirements of any intervening claims, or

they depend from a claim so amended. Accordingly, each of these claims are submitted to be in condition for allowance.

Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the pending claims are in condition for allowance. Accordingly, reconsideration and favorable action on all claims are respectfully requested. Should any issues remain to be resolved in view of the present communication, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that a prompt disposition of the present application can be achieved.

Respectfully submitted,

Date: September 15, 2004

By: _____

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